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KNOWLEDGE OF ENDOCRINE-DISRUPTING CHEMICALS DURING PREGNANCY AND FOETAL DEVELOPMENT

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Abstract

Endocrine-disrupting chemicals are substances that disrupt normal endocrine signaling. On the other hand, the impact of EDCs on the placenta is commonly overestimated. "Fetal growth" is controlled by a complicated mix of "maternal, placental", and foetal factors. EDCs have been linked to foetal growth retardation, thyroid abnormalities, and neurological issues in humans. Endocrine disrupting chemicals (EDCs) primarily interact with insulin, glucocorticoid, estrogenic, and thyroid pathways, resulting in epigenome and inflammatory changes that have long-term effects on normal endocrine and metabolic processes. EDCs evaluated include those present in the environment and for which human biomonitoring data are available.. This study also reveals substantial knowledge gaps that will drive future field research. International scientific organisations recommend that an inquiry be conducted and that all protective measures be implemented.

Keywords: endocrine-disrupting chemicals (EDCs); pregnancy; Growth hormone (GH) ; Human chorionic gonadotropin (HCG); attention deficit hyperactivity disorder (ADHD) ; phthalates ; estrogen receptors (ERs) ; Bisphenol-A (BPA).

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Introduction

Still little understood is the intricate interplay between maternal, placental, and foetal components that regulates foetal growth. The mother's proper intake of "nutrients (carbohydrates, fats, proteins, minerals, vitamins" and oxygen plays a significant role in foetal development, as shown by the altered foetal development found in humans and other animal species when these substances are consumed inadequately or excessively. [1]. However, it is vital to remember that dietary deficit or excess results in observable alterations since endocrine variables primarily regulate foetal development. [1] Insulin-like growth factor is one of the several hormones involved (thyroid hormones, insulin, GH fluctuations, leptin, cortisol (IGF)-1 and IGF-2 are critical [2]. It's also important to remember that the "inflammatory and IGF systems work together ". Other variables, such as Activing, A., Human Chorionic Gonadotropin (HCG), and "Retinoic Acid and its Receptors in Animal Models", have been found and demonstrated to be very important in recent years. [3].

The homeostasis of the systems that govern uterine development has long been recognised as being changed by a number of stressors, potentially raising the "risk of pathological disorders". Maternal illnesses (such as infections, diabetes, or autoimmune diseases), negative lifestyle choices made by the mother (such as using tobacco, alcohol, or narcotics), and/or the use of "therapeutic medications" such as antiepileptic drugs may all impede foetal growth. Many experts have lately examined the influence that widely distributed environmental contaminants may have on the health of the mother [4] and the unborn [5]. The goals of this mini-primary review are as follows.

1. The objective of this study was to update the reader on the current level of knowledge about the interrelationships of endocrine-disrupting chemicals (EDCs), which are synthetic compounds that interfere with the normal functioning of hormones in humans and other animals.
2. Prenatal and postnatal growth and metabolism, as well as the health of pregnant women.

Previous studies and observation

Chemicals are present in all aspects of human existence, including food, the interior environment, cosmetics, and other things that surround us at home and at work. Furthermore, nutritional supplements, pharmaceuticals, and herbal remedies have a chemical influence on the body, which can have both intended and unforeseen consequences. Some substances have been demonstrated to function as endocrine disruptors in laboratory animals among the thousands of chemicals you may be exposed to on a daily basis [6].

These compounds are also thought to interfere with human endocrine function and cause cryptorchidism (undescended testicles to scrotum). In addition, it is associated with low semen quality, a higher risk of testicular cancer, hypoplasia (a genital abnormality) in newborn males, earlier puberty in girls, lower levels of the male sex hormone in men, among other things. Fetal life and childhood are two of the most sensitive phases in a person's life since humans and human bodies are experiencing tremendous development throughout these times, which necessitates a balance of the endocrine systems involved in the various phases of development [7].

Humans are generally exposed to parabens through their usage as preservatives in personal care goods, medications, and food, however they do occur naturally in some fruits and vegetables. [8][9] Parabens are distinguished by their aliphatic or aromatic alkyl moieties, with methylparaben (MePB), ethylparaben (EtPB), propylparaben (PrPB), butylparaben (BuPB), and benzylparaben (BePB) being the most often utilized members of this class of p-hydroxybenzoic acid (PHBA) alkyl esters [10].

A growing body of evidence demonstrating the harmful effects of endocrine-disrupting chemicals (EDCs) has spurred several international scientific and health groups to voice concern about these compounds in recent years. Endocrine Society's 2009 Scientific Statement on EDCs was the first authoritative statement on the subject[11].

At the time, many members of the Society felt there was sufficient evidence to label EDCs a public health crisis. The number of medical associations worldwide expressing concern about EDCs has expanded since the Endocrine Society's original statement in 2009, mirroring the rise in the body of research demonstrating the negative health effects of chemicals that interfere with hormone functioning[6]. In October 2013, the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine issued a joint committee opinion calling for "timely action to detect and minimise exposure to dangerous environmental chemicals." [12].

A Scientific Impact Paper on chemical exposures during pregnancy was published in 2013 by the Royal College of Obstetricians and Gynecologists of the United Kingdom. The purpose of the paper was to "inform pregnant or breastfeeding women of the sources and routes of chemical exposure so that they can take positive action to minimise harm to their unborn child." [13].

Gabriella Morreale de Escobar was one of the pioneering researchers who first proposed the idea that low levels of maternal thyroid hormone (TH) during the early stages of pregnancy may have an effect on the way in which the brain of the unborn child develops [14]. Low and high levels of maternal TH at this period have been linked to increased risk of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), poorer IQ, and decreased grey matter volume. [14]

Experiments conducted on mice and other models of vertebrates have also provided evidence for the concept that maternal TH is necessary for the early development of the brains of vertebrates. Egg yolks of egg-laying vertebrates, including as teleosts, frogs, and birds, have been reported to contain trace amounts of maternal TH. The concept that TH performs tasks that are cell- and time-specific during the early stages of neurogenesis is gaining increasing support within scientific community. In addition, observational studies have shown that even a moderate lack of iodine in the mother is connected to delayed infant brain development as well as a loss in IQ in humans [15].

Human Endocrine system and EDCs

Deficits in any region of the endocrine system may cause sickness or even death since it is engaged in so many critical biological and physiological activities. Infertility, developmental issues, sleep issues, and a number of other chronic and acute diseases are also symptoms of hormonal disruption. To live a healthy life, endocrine hormones must be released at the appropriate amounts, and endocrine glands must be able to adjust hormone release in response to environmental changes..

The Endocrine Society (endocrine.org), the biggest organisation of endocrinology researchers and medical professionals, recently defined EDCs as "an exogenous [non-natural] medication, or combination of chemicals, that interferes with any component of hormone action." [16] Over 85,000 synthetic chemicals are generated each year, many of which potentially be EDCs. Table 2 contains a small selection of typical EDCs and their uses..

There are literally hundreds of different products and processes that also include EDCs, much too many to list in this table..

Table (1): the common EDCS and how they function.

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterial	Triclosan
Textiles, clothing	Perfluorochemicals

Abbreviations: Polychlorinated biphenyls (PCBs), bisphenol A (BPA), 2,4-dichlorophenoxyacetic acid (D2), and DDT are all persistent, toxic, and carcinogenic chemicals..

EDCs may enter the bodies of humans and animals in many different ways (Table 3), such as when they ingest them, when they come into touch with them via the skin, when they are inhaled, and when they are transferred from a pregnant woman to her unborn child over the placenta or when she breastfeeds her newborn.

Table (3): Methods via which people may be exposed to EDCs.

How we are exposed to EDCs	Where the EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or Ground Water	PCBs, dioxins, perfluori nated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food or beverage containers; pesticide residues in food or beverage	BPA, phthalates, Chlorpyrifos, DDT
Contact with skin and/ or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/ or inhalation	Pesticides used in agriculture homes, or for public disease vector control	DDT, Chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Para bens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

Abbreviations: "BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls"

i.Possible mechanism

To comprehend how EDCs disrupt the endocrine system, a basic understanding of how natural hormones function in the body is required. Each endocrine hormone has its own chemical make-up and three-dimensional form. Every hormone has a receptor (or receptors) on the target cells to which it binds. The shape of a receptor is complementary to its hormone, comparable to how one key (hormone) is unique to a lock (receptor).

The response of a tissue or organ to a hormone is characterised by the presence of receptors mostly on target cells and the activation of receptors by hormone binding. The potency and duration of a hormone's activation of its receptor depend on a number of parameters, such as the quantity of hormone generated and released by the endocrine gland, how efficiently the hormone is delivered through the circulatory system, and how much reaches the target organ. play a vital role in ensuring accurate hormone signalling. Each of these steps may be impeded by EDCs. [17].

By mimicking or inhibiting a natural hormone, EDCs frequently damage endocrine systems. In the case of hormone mimics, an EDC can fool the hormone's receptor into believing it's the hormone, causing the receptor to wrongly activate and initiate processes that would typically be triggered only by a natural hormone. An EDC can attach to a hormone's receptor in the case of hormone blockers, but the receptor is blocked and cannot be triggered, even if the natural hormone is present [18].

Most notably, interference with oestrogen and its effects on oestrogen receptors in the body (ERs). Multiple types of cells in the brain, bone, vascular tissues, and reproductive organs of both sexes include ERs. Estrogens have a role in a variety of male physiological processes, including those related to nerve and bone function, cardiovascular health, and more..

Natural estrogens, once they are released from the gonad, will bind to ERs in the " target tissues " , which for females will be the ovary and for males will be the testis [18]. Oestrogen receptors have drawn

the most attention, however EDCs also have other targets. EDCs disrupt the hormone receptors for androgens (testosterone), progesterone, and thyroid hormones. Additionally, because EDCs are synthetic hormones, they may interfere with multiple hormonal signalling pathways. Therefore, it is quite rare for a single EDC to interfere with not just one but multiple endocrine functions, having significant effects on the biological processes that are typically under the delicate control of the endocrine glands [18].

Impacts of EDCs on pregnant

Since 1940, both the supply and the accessibility of manufactured chemicals have skyrocketed, with some of them being discharged (intentionally or not) into the environment. The chemical revolution caused drastic changes in ecosystems that have had negative effects on animal and human healthβ [11].

There have been a lot of research looking at EDCs and pregnant women. Many of them concentrated on one specific molecule. For instance, the content of phthalate metabolites "common plasticizers used in personal care products, textiles, and food packaging) was found to be over the detection limit in at least one sample of urine collected at different times during pregnancy" (LOD). [19].

There was also a lot of research on chemical mixtures. "Polychlorinated biphenyls, organochlorine " insecticides, phenols, perfluorinated chemicals, " polybrominated diphenyl ethers, phthalates, polycyclic aromatic hydrocarbons, and perchlorate" have all been found in between 99 and 100 percent of pregnant women's urine tests. Four to twelve perfluorinated compounds and nine to thirteen phthalates were found to be the most frequently occurring groups of chemicals. [20].

Different EDC levels were observed according on the season [21], ethnic groupings [22], occupation type [23], and socioeconomic circumstances [24]. It was also shown that EDCs may be present in both pregnant and non-pregnant women, illustrating their widespread environmental dissemination. [20].

Several authors have brought up the placenta's potential impact on maternal and foetal health, both immediately and in the future. Polybrominated biphenyl ethers (PBDEs) are flame retardants that are used in the manufacturing of many everyday things, including electronics, furniture, textiles, foam, and plastics. They have also been linked to the disruption of normal placental development. [25].

We still don't know how exactly EDCs change placental structure and function. However, a number of studies have proposed several explanations. The Thr1 and Thr1 genes are responsible for producing thyroid hormone receptors (THRs), which play an important role in regulating placental development. [26].

The downregulation of the Thrβ1 and Thrα1 genes as well as the suppression of "nuclear translocation" in the placenta are both influenced by phthalate exposure in animal models [26]. In addition, exposure to polybrominated diphenyl ethers and polycyclic aromatic hydrocarbons (PAHs) alters the concentration of IGF-1 in the placenta (PBDEs) [27].

Pathogenic effect and possible mechanism

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, prenatal exposure might cause epigenetic changes that affect fetal programming and increase the risk of several noncommunicable diseases later in life.[28]. These alterations may be brought on by single EDCs or mixtures (as was previously mentioned), and single EDCs or mixes may also interact with the inflammasome during pregnancy[29].

The placenta was discovered to contain polychlorinated biphenyls (PCBs) from a variety of sources, including pesticides, "personal care products, polybrominated diphenyl ethers, bisphenol A", and others. [30] Phthalates affect "placental growth and development" in pregnant mice, and they also pass the feto-placental barrier. [31].

Zhu et al. [32], who examined maternal urine phthalate excretion throughout all three trimesters of pregnancy, found that prenatal exposure to phthalates was associated with altered placental size and shape in humans. Certain phthalates were discovered to have the capacity to increase placental thickness and produce a more circular placenta. Similarly, males seemed to have stronger connections. This latest finding lends credence to the theory that placental abnormalities are at the root of many health problems and gender differences. [33].

Recent studies have shown that DNA methylation is sensitive to environmental factors, which might alter the human placenta's methylome, resulting in abnormal placental growth and function and potentially altering the pregnancy's outcome. Some environmental factors, such cadmium, air pollution, and tobacco use, may play a role in this. [34]. Interleukin (IL)-6 levels during the first trimester and environmental EDC exposure have been linked, according to Kelley et al. [35]. The correlation between elevated IL-6 and decreased " IGF bioavailability" in the placenta and foetal development limitation suggests[36 "an additional pathogenetic mechanism" that may not be only induced by hypoxia, as was previously believed] [37] .

Recent studies [34] have shown that a number of environmental variables, including as smoking, air pollution, and cadmium, have the potential to influence the human placental methylome, which may lead to abnormal placental growth and function.. It is well known that microRNAs may affect how genes are expressed and that they can change when there is cancer or inflammation [38]. Additionally, "there is growing evidence "that exposure to EDC and prenatal factors both contribute to the development of cancer later in life. [39].

There is growing evidence that the effects of TH disruptors on brain development are connected to the capacity of these agents to alter the amounts of intracellular TH availability and hence deregulate transcription and TH-induced epigenetic changes on target genes. Blocking iodine uptake, inhibiting TH production, displacing T4 and T3 from TH-distributing proteins, stimulating hepatic metabolism[5], lowering circulating TH levels, interfering with transmembrane cellular transporters (MCT8 and OATP1C1), altering deiodinase enzyme activities, and, less commonly, straightforwardly acting at the threshold of the TR ligand-binding pocket or domain are all examples of methods for interfer (LBD) [40].

The effect of some EDCs

Phthalates are a family of chemicals that are widely used in production and are afterwards present in many commonplace items. Phthalates are a class of chemicals that may be found in a wide range of common consumer goods, such as IV tubing and vinyl flooring. Some of these phthalates have been demonstrated to have estrogenic activity and anti-androgenic properties. Prenatal and early postnatal exposure to high quantities of some environmental toxins can harm the baby and child's health, with long-term consequences into adulthood.

One of the most important genes in early placental development is the epidermal growth factor receptor (EGFR), which has been shown to influence gene methylation and expression. There was an inverse correlation between placental IGF-2 DNA methylation and "urinary concentrations of mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP) " in infants with foetal growth restriction (FGR) [42]. Insulin-like growth factor 2 is a key regulator of foetal and placental growth. [43].

DDTs: is a kind of organochlorine pesticide that saw extensive global usage in the postwar decades of the 1940s, 1950s, and 1960s. Insecticides were used in industrial and home farming, in addition to gardens, parks, and other public and private spaces, and in institutions. Most of the world's population continues to consume food tainted with DDT.

Since DDTs are deposited in animal fats, these foods tend to have the greatest amounts of DDTs, especially "meat, fish, poultry, eggs, cheese, butter, and milk". DDTs continue to be a major cause of food poisoning, and in regions where DDT is actively used and manufactured, levels may rise to dangerous heights. Fetuses are vulnerable to infection via placental transfer, and breastfed infants are at risk as well. [37].

POPs, DDTs, for example, have been connected to alterations in the methylation of many genes, including the" IGF-2 gene". [43].

Bisphenol :"A (BPA) ": The possibility of human exposure to an estrogen-like chemical that may leak from consumer items. Polycarbonate, epoxy resins, and other commonplace items were expected to use 2.3 billion pounds. [1] . The vast majority of BPA items have some kind of interaction with either food or drink. There is a danger of human exposure to BPA if the product is exposed to heat or acid, or if it includes residual monomers. [44].

Oral consumption, inhalation, and cutaneous exposure are the three modes of exposure. BPA has also been found in umbilical cord blood (0.2–9.2 ng/mL), demonstrating that BPA is transported across the placental barrier, in placental tissue (up to 104.9 ng/g), and in amniotic fluid (0–8.38 ng/mL)[3][45].

A larger ratio of the BPA "levels in the amniotic fluid" to the concentration in the maternal plasma in pair-matched samples has also been associated with a lower birth weight [46]. In vitro studies have shown that BPA has substantial endocrine activity through oestrogen and androgen receptors, and BPA has been shown to interact with all known human oestrogen receptor subtypes .[19] Premature puberty is measured as vaginal opening in tiny mice after in utero exposure to 2.4 g BPA/kg bodyweight/d.[20[

BPA prenatal and postnatal exposure to 250 ng/kg-d and 50 g/kg-d, respectively, interfered with the "proper development of reproductive organs" and mammary glands in female and male mice [47].

The effects of BPA exposure on the trophoblast-derived BeWo choriocarcinoma cell line and explants from first trimester human placentae were studied in one study. Furthermore, full-term placenta transport tests, BeWo cell monolayers, and experiments on BPA percutaneous penetration were used to examine fetal bioavailability. [48] According to Merck et al. [49], BPA is transported through the placenta and increases -HCG, hence affecting placental development. Some researchers found that BPA levels in trophoblast cells during the first trimester of pregnancy disrupted normal cellular development and altered DNA methylation. [50].

Parabens

The US Food and Drug Administration has not raised any safety concerns about the use of parabens, which are used as preservatives in cosmetics and personal care items. [51] One pharmacokinetic study in pregnant rats [52] indicated that there was twice as much ethylparaben in the placenta as in the foetal liver, pointing to placental accumulation, but no further investigations have been done on humans during pregnancy. A recent in vitro research using HTR-8/SVneo cells showed that exposure to butylparaben inhibits cell development, and increases apoptosis and endoplasmic reticulum (ER) stress (200 M). [53] Worldwide, paraben exposure during pregnancy is second only to that of phthalates..

"Triclosan (TCS) and triclocarban" (TCC),

In one study, TCS was found in all participants and was found in a variety of consumer goods including soaps, toothpaste, medical equipment, plastics, and textiles. [40]. Paraben metabolites, a popular preservative used for decades, have been found in as much as 100% of maternal urine samples, and recent study has demonstrated that they are endocrine disruptors, especially in infants.. [22].

EDCs During Pregnancy and Their Postnatal Effects

Cognitive and behavioural differences between men and females were studied by Ejaredar et al. (2015), who looked at whether or not prenatal exposure to phthalate metabolites changed dependent on molecular weight.. The incidence of adverse cognitive and behavioural outcomes was shown to be higher in men who were treated to LMW metabolites during pregnancy, while the incidence of such outcomes was found to be higher in females who were exposed to HMW metabolites. [54] However, Kim et al. discovered that exposure to juvenile phthalates, not maternal phthalates, was linked to a negative impact on IQ and attentional performance in six-year-old children. [55].

Additionally, in long-term studies starting with pregnancy, it indicates that the relationship between phthalate exposure with development is more significant in the postnatal period (especially at three years of age). [56]. In a more recent meta-analysis, it was shown that phthalate exposure is more dangerous throughout youth than during pregnancy (as determined by urine DHEP [di-(2 ethylhexyl) phthalate]). The psychomotor developmental index fell 0.6 points when maternal urine levels doubled during

pregnancy, and IQ dropped 0.8 points when levels doubled throughout childhood (PDI) [57].

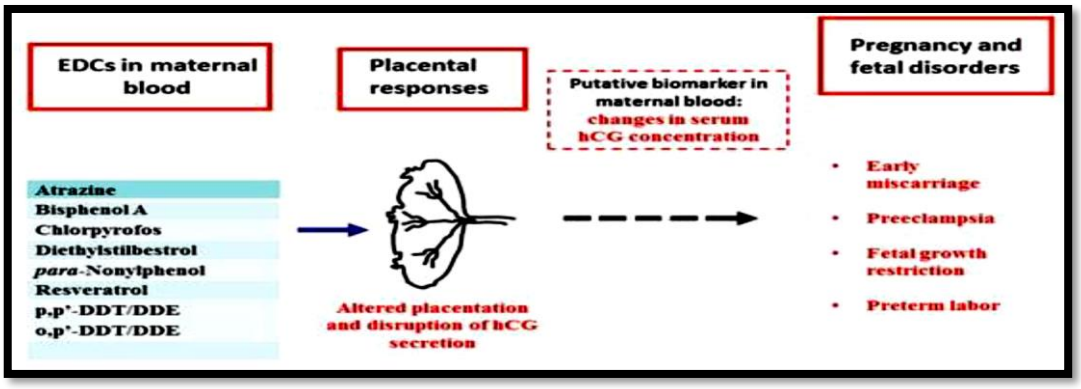

Figure 1: Explains the role of EDCs in infertility [3].

The prevention and control

The "International Federation of Gynecology and Obstetrics (FIGO) has recently published an opinion piece" entitled "Opinion on the Consequences of Toxic Environmental Chemicals on Reproductive Health.". [9]. According to a "precautionary" approach to reducing risk in the absence of causal evidence, the Royal College of Obstetricians and Gynecologists concluded that "despite uncertainty surrounding the effects of common environmental chemicals, mothers should be made aware of the sources and routes of exposure, the potential risks to the fetus/baby, and the important role that the mother can play in minimizing her baby's chemical exposure".

These suggestions appear to take on an even greater level of significance in light of recent survey findings that were not very encouraging. According to the findings of study conducted by "Rouillon et al., 54.3% of 300 French mothers" who were visited during pregnancy or the " first few days after giving birth indicated" that they never heard of EDCs. [58]

In Canada, there was also a lack of understanding of the potential hazards associated with EDC exposure.[59].Furthermore, only a small percentage of medical practitioners who accompany expectant moms devote enough time to teaching them on how to avoid environmental dangers, making them feel culturally unfit for the job[60].

As a result, it has been suggested that more resources be allotted toward the "pre- and post-graduate" "training of physicians", particularly obstetricians, and that public awareness campaigns be implemented with the necessary laws and public health initiatives. In addition, it has been suggested that more resources be allotted toward the research and development of new treatments.. [61].

References

[1] A. N. Sferruzzi-Perri, O. R. Vaughan, A. J. Forhead, and A. L. Fowden, "Hormonal and nutritional drivers of intrauterine growth.," Curr. Opin. Clin. Nutr. Metab. Care, vol. 16, no. 3, pp. 298–309, May 2013, doi: 10.1097/MCO.0b013e32835e3643.

[2] M. E. Street et al., "Interleukin-6 and insulin-like growth factor system relationships and differences in the human placenta and fetus from the 35th week of gestation." Growth Horm. IGF Res. Off. J. Growth Horm. Res. Soc. Int. IGF Res. Soc., vol. 16, no. 5–6, pp. 365–372, 2006, doi: 10.1016/j.ghir.2006.09.007.

[3] L. Paulesu, C. V. Rao, F. Ietta, A. Pietropolli, and C. Ticconi, "hCG and Its Disruption by Environmental Contaminants during Human Pregnancy," International Journal of Molecular Sciences , vol. 19, no. 3. 2018, doi: 10.3390/ijms19030914.

[4] J. Varshavsky et al., "Heightened susceptibility: A review of how pregnancy and chemical exposures influence maternal health," Reprod. Toxicol., vol. 92, pp. 14–56, 2020, doi: https://doi.org/10.1016/j.reprotox.2019.04.004.

[5] G. C. Di Renzo et al., "International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals," Int. J. Gynecol. Obstet., vol. 131, no. 3, pp. 219–225, Dec. 2015, doi: https://doi.org/10.1016/j.ijgo.2015.09.002.

[6] Miljøstyrelsen, "Exposure of pregnant consumers to suspected endocrine disruptors," Miljøstyrelsen Strandgade 29 1401 København K www.mst.dk, 2012.

[7] B. B. Mughal, J.-B. Fini, and B. A. Demeneix, "Thyroid-disrupting chemicals and brain development: an update," Endocr. Connect. vol. 7, no. 4, pp. R160–R186, Apr. 2018, doi: 10.1530/EC-18-0029.

[8] C. Liao and K. Kannan, "Concentrations and composition profiles of parabens in currency bills and paper products including sanitary wipes," Sci. Total Environ., vol. 475, pp. 8–15, 2014, doi: https://doi.org/10.1016/j.scitotenv.2013.12.097.

[9] C. Liao, F. Liu, and K. Kannan, "Occurrence of and Dietary Exposure to Parabens in Foodstuffs from the United States," Environ. Sci. Technol., vol. 47, no. 8, pp. 3918–3925, Apr. 2013, doi: 10.1021/es400724s.

[10] D. Błędzka, J. Gromadzińska, and W. Wąsowicz, "Parabens. From environmental studies to human health," Environ. Int., vol. 67, pp. 27–42, 2014, doi:

https://doi.org/10.1016/j.envint.2014.02.007.

[11] E. Diamanti-Kandarakis et al., "Endocrine-disrupting chemicals: an Endocrine Society scientific statement." Endocr. Rev., vol. 30, no. 4, pp. 293–342, Jun. 2009, doi: 10.1210/er.2009-0002.

[12] B. Haruty, J. Friedman, S. Hopp, R. Daniels, and J. Pregler, "Reproductive health and the environment: Counseling patients about risks," Cleve. Clin. J. Med., vol. 83, no. 5, pp. 367 LP – 372, May 2016, doi: 10.3949/ccjm.83a.14070.

[13] R. C. of O. and Gynaecologists, "Chemical Exposures During Pregnancy: Dealing with Potential, but Unproven, Risks to Child Health," 2013.

[14] G. Escobar, M.-J. Obregon, and F. Rey, "Role of thyroid hormone during early brain development," Eur. J. Endocrinol., vol. 151 Suppl, pp. U25-37, Dec. 2004, doi: 10.1530/eje.0.151U025.

[15] B. A. Demeneix, "Evidence for Prenatal Exposure to Thyroid Disruptors and Adverse Effects on Brain Development," Eur. Thyroid J., vol. 8, no. 6, pp. 283–292, 2019, doi: 10.1159/000504668.

[16] R. T. Zoeller et al., "Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society.," Endocrinology, vol. 153, no. 9, pp. 4097–4110, Sep. 2012, doi: 10.1210/en.2012-1422.

[17] N. E. Skakkebaek, J. Toppari, O. Söder, C. M. Gordon, S. Divall, and M. Draznin, "The exposure of fetuses and children to endocrine disrupting chemicals: a European Society for Paediatric Endocrinology (ESPE) and Pediatric Endocrine Society (PES) call to action statement.," J. Clin. Endocrinol. Metab., vol. 96, no. 10, pp. 3056–3058, Oct. 2011, doi: 10.1210/jc.2011-1269.

[18] D. S. Gore AC, "Endocrine Disruptors and the Developing Brain:," Morgan & Claypool;, 2012.

[19] T. E. Arbuckle et al., "Maternal and early life exposure to phthalates: The Plastics and Personal-care Products use in Pregnancy (P4) study," Sci. Total Environ., vol. 551–552, pp. 344–356, 2016, doi: https://doi.org/10.1016/ j.scitotenv.2016.02.022.

[20] W. T. J., Z. A. R., and S. J. M., "Environmental Chemicals in Pregnant Women in the United States: NHANES 2003–2004," Environ. Health Perspect., vol. 119, no. 6, pp. 878–885, Jun. 2011, doi: 10.1289/ehp.1002727.

[21] H. Gao et al., "Season-dependent concentrations of urinary phthalate metabolites among Chinese pregnant women: Repeated measures analysis." Environ. Int., vol. 104, pp. 110–117, Jul. 2017, doi: 10.1016/j.envint.2017.03.021.

[22] B. F. G. Pycke, L. A. Geer, M. Dalloul, O. Abulafia, and R. U. Halden, "Maternal and fetal exposure to parabens in a multiethnic urban U.S. population.," Environ. Int., vol. 84, pp. 193–200, Nov. 2015, doi: 10.1016/j.envint.2015.08.012.

[23] B. Laura et al., "Occupational Exposure to Endocrine-Disrupting Chemicals and Birth Weight and Length of Gestation: A European Meta-Analysis," Environ. Health Perspect., vol. 124, no. 11, pp. 1785–1793, Nov. 2016, doi: 10.1289/EHP208.

[24] W.-C. Lee, M. Fisher, K. Davis, T. E. Arbuckle, and S. K. Sinha, "Identification of chemical mixtures to which Canadian pregnant women are exposed: The MIREC Study.," Environ. Int., vol. 99, pp. 321–330, Feb. 2017, doi: 10.1016/j.envint.2016.12.015.

[25] Y. Zhao et al., "Umbilical cord blood PBDEs concentrations in relation to placental size at birth," Chemosphere, vol. 201, pp. 20–24, 2018, doi: https://doi.org/10.1016/j.chemosphere.2018.02.121.

[26] Z. Yu et al., "Gestational di-(2-ethylhexyl) phthalate exposure causes fetal intrauterine growth restriction through disturbing placental thyroid hormone receptor signaling," Toxicol. Lett. vol. 294, pp. 1–10, 2018, doi: https://doi.org/10.1016/j.toxlet.2018.05.013.

[27] X. Xu, T. A. Yekeen, Q. Xiao, Y. Wang, F. Lu, and X. Huo, "Placental IGF-1 and IGFBP-3 expression correlate with umbilical cord blood PAH and PBDE levels from prenatal exposure to electronic waste," Environ. Pollut., vol. 182, pp. 63–69, 2013, doi: https://doi.org/10.1016/j.envpol.2013.07.005.

[28] D. J. P. Barker and C. Osmond, "INFANT MORTALITY, CHILDHOOD NUTRITION, AND ISCHAEMIC HEART DISEASE IN ENGLAND AND WALES," Lancet, vol. 327, no. 8489, pp. 1077–1081, May 1986, doi: 10.1016/S0140-6736(86)91340-1.

[29] N. Vilahur et al., "Prenatal exposure to mixtures of xenoestrogens and genome-wide DNA methylation in human placenta.," Epigenomics, vol. 8, no. 1, pp. 43–54, Jan. 2016, doi: 10.2217/epi.15.91.

[30] C. Yang, G. Song, and W. Lim, "A mechanism for the effect of endocrine disrupting chemicals on placentation," Chemosphere, vol. 231, pp. 326–336, 2019, doi: https://doi.org/10.1016/j.chemosphere.2019.05.133.

[31] T. Zong et al., "Maternal exposure to di-(2-ethylhexyl) phthalate disrupts placental growth and development in pregnant mice." J. Hazard. Mater. vol. 297, pp. 25–33, Oct. 2015, doi: 10.1016/j.jhazmat.2015.04.065.

[32] Y.-D. Zhu et al., "Prenatal phthalate exposure and placental size and shape at birth: A birth cohort study." Environ. Res., vol. 160, pp. 239–246, Jan. 2018, doi: 10.1016/j.envres.2017.09.012.

[33] A. Gabory, T. J. Roseboom, T. Moore, L. G. Moore, and C. Junien, "Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics.," Biol. Sex Differ., vol. 4, no. 1, p. 5, Mar. 2013, doi: 10.1186/2042-6410-4-5.

[34] A. Vlahos, T. Mansell, R. Saffery, and B. Novakovic, "Human placental methylome in the interplay of adverse placental health, environmental exposure, and pregnancy outcome," PLOS Genet., vol. 15, no. 8, p. e1008236, Aug. 2019, [Online]. Available: https://doi.org/10.1371/journal.pgen.1008236.

[35] A. S. Kelley et al., "Early pregnancy exposure to endocrine disrupting chemical mixtures are associated with inflammatory changes in maternal and neonatal circulation," Sci. Rep., vol. 9, no. 1, p. 5422, 2019, doi: 10.1038/s41598-019-41134-z.

[36] M. E. Street et al., "Changes in interleukin-6 and IGF system and their relationships in placenta and cord blood in newborns with fetal growth restriction compared with controls," Eur. J. Endocrinol. eur j endocrinol, vol. 155, no. 4, pp. 567–574, doi: 10.1530/eje.1.02251.

[37] A. Smerieri, M. Petraroli, M. A. Ziveri, C. Volta, S. Bernasconi, and M. E. Street, "Effects of Cord Serum Insulin, IGF-II, IGFBP-2, IL-6 and Cortisol Concentrations on Human Birth Weight and Length: Pilot Study," PLoS One, vol. 6, no. 12, p. e29562, Dec. 2011, [Online]. Available: https://doi.or /10.1371/journal.pone.0029562.

[38] F. Cirillo, C. Catellani, C. Sartori, P. Lazzeroni, S. Amarri, and M. E. Street, "Obesity, Insulin Resistance, and Colorectal Cancer: Could miRNA Dysregulation Play a Role?," International Journal of Molecular Sciences , vol. 20, no. 12. 2019, doi: 10.3390/ijms20122922.

[39] M. E. Street et al., "Current Knowledge on Endocrine Disrupting Chemicals (EDCs) from Animal Biology to Humans, from Pregnancy to Adulthood: Highlights from a National Italian Meeting," International Journal of Molecular Sciences , vol. 19, no. 6. 2018, doi: 10.3390/ijms19061647.

[40] B. F. G. Pycke, L. A. Geer, M. Dalloul, O. Abulafia, A. M. Jenck, and R. U. Halden, "Human Fetal Exposure to Triclosan and Triclocarban in an Urban Population from Brooklyn, New York," Environ. Sci. Technol., vol. 48, no. 15, pp. 8831–8838, Aug. 2014, doi: 10.1021/es501100w.

[41] N. M. Grindler et al., "Exposure to Phthalate, an Endocrine Disrupting Chemical, Alters the First Trimester Placental Methylome and Transcriptome in Women," Sci. Rep., vol. 8, no. 1, p. 6086, 2018, doi: 10.1038/s41598-018-24505-w.

[42] Y. Zhao, J. Chen, X. Wang, Q. Song, H.-H. Xu, and Y.-H. Zhang, "Third trimester phthalate exposure is associated with DNA methylation of growth-related genes in human placenta," Sci. Rep., vol. 6, no. 1, p. 33449, 2016, doi: 10.1038/srep33449.

[43] S. Kim et al., "Prenatal exposure to persistent organic pollutants and methylation of LINE-1 and imprinted genes in placenta: A CHECK cohort study," Environ. Int., vol. 119, pp. 398–406, 2018, doi: https://doi.org/10.1016/j.envint.2018.06.039.

[44] M. J. J. Finken et al., "Children Born Small for Gestational Age: Differential Diagnosis, Molecular Genetic Evaluation, and Implications," Endocr. Rev., vol. 39, no. 6, pp. 851–894, Dec. 2018, doi: 10.1210/er.2018-00083.

[45] E. Bloise, P. Ciarmela, C. Dela Cruz, S. Luisi, F. Petraglia, and F. M. Reis, "Activin A in Mammalian Physiology," Physiol. Rev., vol. 99, no. 1, pp. 739–780, Dec. 2018, doi: 10.1152/physrev.00002.2018.

[46] Y. Suzuki, M. Niwa, J. Yoshinaga, Y. Mizumoto, S. Serizawa, and H. Shiraishi, "Prenatal exposure to phthalate esters and PAHs and birth outcomes," Environ. Int., vol. 36, no. 7, pp. 699–704, 2010, doi: https://doi.org/10.1016/j.envint.2010.05.003.

[47] M. Muñoz-de-Toro et al., "Perinatal exposure to bisphenol-A alters peripubertal

mammary gland development in mice.," Endocrinology, vol. 146, no. 9, pp. 4138–4147, Sep. 2005, doi: 10.1210/en.2005-0340.

[48] H. Yamada et al., "Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester.," Reprod. Toxicol., vol. 16, no. 6, pp. 735–739, 2002, doi: 10.1016/s0890-6238(02)00051-5.

[49] T. J. Mørck et al., "Placental transport and in vitro effects of Bisphenol A," Reprod. Toxicol., vol. 30, no. 1, pp. 131–137, 2010, doi: https://doi.org/10.1016/j.reprotox.2010.02.007.

[50] S. Basak, V. Srinivas, and A. K. Duttaroy, "Bisphenol-A impairs cellular function and alters DNA methylation of stress pathway genes in first trimester trophoblast cells," Reprod. Toxicol., vol. 82, pp. 72–79, 2018, doi: https://doi.org/10.1016/j.reprotox.2018.10.009.

[51] N. Halla et al., "Cosmetics Preservation: A Review on Present Strategies," Molecules , vol. 23, no. 7. 2018, doi: 10.3390/molecules23071571.

[52] H. Frederiksen, C. Taxvig, U. Hass, A. M. Vinggaard, and C. Nellemann, "Higher Levels of Ethyl Paraben and Butyl Paraben in Rat Amniotic Fluid than in Maternal Plasma after Subcutaneous Administration," Toxicol. Sci., vol. 106, no. 2, pp. 376–383, Dec. 2008, doi: 10.1093/toxsci/kfn171.

[53] C. Yang, W. Lim, F. W. Bazer, and G. Song, "Butyl paraben promotes apoptosis in human trophoblast cells through increased oxidative stress-induced endoplasmic reticulum stress.," Environ. Toxicol., vol. 33, no. 4, pp. 436–445, Apr. 2018, doi: 10.1002/tox.22529.

[54] M. Ejaredar, E. C. Nyanza, K. Ten Eycke, and D. Dewey, "Phthalate exposure and childrens neurodevelopment: A systematic review," Environ. Res., vol. 142, pp. 51–60, 2015, doi: https://doi.org/10.1016/j.envres.2015.06.014.

[55] J. I. Kim, Y.-C. Hong, C. H. Shin, Y. A. Lee, Y.-H. Lim, and B.-N. Kim, "The effects of maternal and children phthalate exposure on the neurocognitive function of 6-year-old children," Environ. Res., vol. 156, pp. 519–525, 2017, doi: https://doi.org/10.1016/j.envres.2017.04.003.

[56] N. Li et al., "Identifying periods of susceptibility to the impact of phthalates on

Children's cognitive abilities," Environ. Res., vol. 172, pp. 604–614, 2019, doi: https://doi.org/10.1016/j.envres.2019.03.009.

[57] D.-W. Lee, M.-S. Kim, Y.-H. Lim, N. Lee, and Y.-C. Hong, "Prenatal and postnatal exposure to di-(2-ethylhexyl) phthalate and neurodevelopmental outcomes: A systematic review and meta-analysis," Environ. Res., vol. 167, pp. 558–566, 2018, doi: https://doi.org/10.1016/j.envres.2018.08.023.

[58] S. Rouillon et al., "Endocrine Disruptors and Pregnancy: Knowledge, Attitudes and Prevention Behaviors of French Women," International Journal of Environmental Research and Public Health , vol. 14, no. 9. 2017, doi: 10.3390/ijerph14091021.

[59] A. Lane et al., "Pregnant Women's perceptions of exposure to brominated flame retardants," Reprod. Health, vol. 13, no. 1, p. 142, 2016, doi: 10.1186/s12978-016-0257-2.

[60] C. Marie, D. Lémery, F. Vendittelli, and M.-P. Sauvant-Rochat, "Perception of Environmental Risks and Health Promotion Attitudes of French Perinatal Health Professionals," International Journal of Environmental Research and Public Health , vol. 13, no. 12. 2016, doi: 10.3390/ijerph13121255.

[61] M. E. Street and S. Bernasconi, "Endocrine-Disrupting Chemicals in Human Fetal Growth.," Int. J. Mol. Sci., vol. 21, no. 4, Feb. 2020, doi: 10.3390/ijms21041430.